REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

The specification has been amended in its first paragraph to update the status of parental applications. Claims 1, 11 and 25 have been amended. Claims 1-46 are in the case and are before the Examiner.

A. The Amendments

The specification has been amended to up-date the status of the parental applications.

Claims 1, 11 and 25 have been amended to clarify the sequences and linkages that are or can be located between residues at about position 76 through about position 85. These amendments largely rearrange the words present originally.

Claims 1 and 11 have been amended to positively recite the presence of a peptide-bonded heterologous sequence at one or more of the N-terminus, in the HBc immunodominant loop and at the C-terminus of the chimer. Claim 25 has been amended to more particularly recite that up to 60 amino acid residues are peptide-bonded to HBc residue 75 of Domain I as recited at page 39 of the specification and to further identify what those up to about 60 residues are as disclosed at page 40 of the specification.

Claims 1 and 25 have also been amended in the portion relating to Domain IV to recite that the formed particles "exhibit a ratio of absorbance at 280 nm to 260 nm of about 0.9 to about 1.7" as is recited in claim 11, as well as at least in the first paragraph of page 34 and at page 47. The word "about"

has been added to claim 11 so that the language of the claims is the same. Claim 25 has been amended in the recitation of Domain II to clarify that HBc residue 85 is present as noted by the recitations related to Domain III. Thus, the word "to" has been used to replace the word "through". Each of claims 1, 11 and 25 has also been amended to clarify the base sequence (SEQ ID NO:1) against which the percentage of substitution is calculated. Support for this amendment can be found at pages 74-76.

Claim 1 has also been amended in sub-paragraph (b)(i) to recite "a sequence of 1 to about 40 residues … " as compared to "a sequence of up to about 40 residues … ". This amendment is supported at least in the disclosures of the first full paragraph of page 31.

The claims have also been reformatted to better assist in their understanding per the Examiner's helpful suggestion.

It is thus seen that no new matter has been added.

B. Rejection Under 35 USC §112, Second Paragraph

Claims 1, 11 and 25 were rejected as allegedly indefinite and ambiguous in Paragraph 1 due to their inclusion of alternatives. Changes in format were also requested so that the reader could better understand what is being claimed. As noted above, those clarifying amendments have been made. It is therefore believed this basis for rejection is moot. The discussion that follows in response to the Examiner's comments should further clarify the claimed subject matter.

In regard to claim 1 part (b)(i), discussed in Paragraph 2, the action asserts that it makes no sense to say zero residues are present and asks if none are present, what is

peptide-bonded to the one of about 245 amino acids? Zero residues present is simply one extreme and if no residues of that region are present, one need only to note that residue 75 is present at the C-terminus of the sequence so that is the residue to which an insert would be bonded. The Examiner's attention on this point is directed to the full paragraph on page 63.

The Examiner is correct that because of the presence of the word "or", some residues can be present and others replaced. It is believed that the present reformatting of the claim should assist in understanding the various alternatives, and this rejection should therefore be withdrawn.

Paragraph 3 of this section asks about the word "optionally" in part (b) of claims 1 and 11. It is believed that this basis for rejection is moot in view of the amendments.

In paragraph 4 of this section, the Action asserts that use of the parenthesized "(in the immunodominant loop)" does not define the boundaries of the loop. The claim has been amended to speed prosecution.

Paragraph 5 of this section asserts that a definition is needed for the word "substituted". It is submitted that that word is used in its usual English meaning, e.g., replaced, so that even a judge uneducated in biochemistry would be able to understand its use.

This paragraph also asserts an inconsistency in the use of "conservatively substituted" in that it is asserted that a worker of ordinary skill in this art to whom this specification is directed would not know what a biologically similar residue is. The Action noted a definition at page 25. The Examiner's attention on this point is also directed to the

text of the first paragraph of page 73 through the top of page 74.

The asserted inconsistency appears to relate to counting a deletion or truncation as a conservative substitution. The gist of this portion of the rejection appears to be that when the percentage of allowable substitutions or numbers of substituting residues in an HBc sequence is discussed at pages 74-75 in regard to how to treat deletions, the person of skill in this art to whom the invention is directed was instructed to deem a deletion as a conservative substitution when calculating the percentage of substitution.

Once the context surrounding that discussion is read completely and that text is understood to be for the purpose of calculating the percentage or number of allowable substitutions, there is neither inconsistency nor is there indefiniteness. Furthermore, inasmuch as a patentee can be his own lexicographer, the applicant is free to further define his definition of a "conservative substitution" in that it is not misleading, and is straight-forward. As such, this basis for rejection should be withdrawn.

The Action continued by asserting a lack of clarity as to which sequence one uses to determine a conservative substitution. This assertion lacks merit in that several mammalian HBc sequences are disclosed and can be used, and the plain language of the text is clear to a skilled worker. It appears as though the Action is really trying to assert a breadth rejection in the guise of alleged indefiniteness, but breadth is not indefiniteness. *In re Gardner*, 166 USPQ 138 (CCPA 1970).

It is agreed that the subtype *ayw* sequence shown in Fig. 1 (SEQ ID NO:1), is preferred and is used to determine the percentage of substitution. On the other hand, the other human subtype sequences can be used as can a sequence from another mammal. The Examiner's attention on this point is invited to the paragraph bridging pages 35-36. Examination of Fig. 1 illustrates the similarities between the several sequences and use of any would be no problem to a skilled worker. In addition, should a worker choose to use residues of positions 1-80 of one sequence linked to the residues of positions 81-149 or 156 of another sequence, as indicated in the allegedly vague disclosure, even a non-skilled worker would be able to determine that fact by simply looking at the sequences of Fig. 1. Thus, this basis for rejection should be withdrawn.

Paragraph 6 of this section asserts an ambiguity in claim 25, in the subsection dealing with Domain IV that originally included the sub-paragraph related to nine arginines and lysines. That sub-paragraph has been amended to provide added clarity. However, the Action asks whether the sequence could contain "a mixture of nine arginines and nine lysines or can the total of the residues not exceed nine?" The answer is less than a total of ten lysines and arginines together, as was indicated by the recitation "or mixtures thereof" at the end of the phrase and the last sentence of the paragraph bridging pages 47 and 48. It is believed that the remainder of the paragraph is moot.

It is believed that Paragraph 7 of this section is moot in view of the present amendments.

Paragraph 8 asserts that the term "more stable" is indefinite in that a standard is said not to be present for the

skilled worker to determine the scope of the invention. The Action asserts that one cannot determine if one molecule is more stable than another.

In this regard, the Examiner's attention is invited to the last two paragraphs of page 49 where he finds that one can use "analytical size exclusion chromatography and upon analysis by non-reducing SDS-PAGE" and that the reader is directed to the Examples. The Examiner's attention is next invited to Example 1D that begins near the bottom of page 148 wherein analytical size exclusion chromatography and non-reducing SDS-PAGE are discussed, and then to Examples 9 and 10 and Fig.4 wherein differences are shown graphically. As is noted at page 149:

> [p]article integrity was assessed by visualization of peak elution profiles, where the presence of one peak at an elution position of approximately 7 mL is fully formed particle. Later peaks represent non-particulate structures, such as dimers and monomers.

The skilled worker only needs to look at the profiles in Fig.4 to see that a comparison is all that is needed. As such, this rejection should be withdrawn.

Paragraph 9 of this section asserts claims 1, 11 and 25 to be indefinite because of their use of one or the other of "of at least about" and "up to about". It cannot be agreed that the use of "of at least about" made any of the claims that contained that phrase indefinite, nor can it be agreed that the use of the phrase "up to about" made any of the claims indefinite.

Attached Exhibit 1 is a copy of a search made by the undersigned of the US Patent Office data base in which

presumptively valid US patents with claims that contain the phrase "at least about" were sought, whereas attached Exhibit 2 is a similar search result in the US patent Office data base in which the presence of the complained of phrase "up to about" in issued US patent claims was assayed. As is seen from the attached, more than 60,000 presumptively valid US patents have issued since 1976 that contain one or more claims that include the phrase "at least about", whereas more than 23,000 presumptively valid US patents have issued since 1976 that contain claims that include the complained of phrase. Examination of the patents indicates that at least one in each group issued on Tuesday, May 10, 2005.

In addition, Exhibit 3 lists 37 presumptively valid patents issued since 1976 that have one or more claims tht contain the phrase "up to about" in which the Primary Examiner was Mr. James Housel, the Primary Examiner here. Exhibit 4 lists 15 presumptively valid patents on which Mr. Housel served as Primary Examiner whose claims include the phrase "at least about". Further examination shows that the two phrases are used in those patent claims as they are here. It is respectfully submitted that the phraseology of issued patent claims is *prime facie* evidence of language that is not indefinite, and as such, this basis for rejection should be withdrawn.

Paragraph 10 noted a potential ambiguity in claim 25 where it might be possible that residue 85 were absent as recited in relation to Domain II but needed in Domain III. Inasmuch as Domain III requires that residue 85 be present and Domain II only suggests that that residue might be absent in some constructs, the claims have been amended to rely upon the

required element, the presence of residue 85 by reciting that "zero to all of the sequence of HBc is present from position 76" to rather than through 85. It is believed this basis for rejection is moot and should be withdrawn.

C. Rejection Under 35 USC §112, First Paragraph

All of the claims were rejected under the first paragraph of Section 112 as allegedly failing the description requirement and the enablement requirement. As is discussed hereinafter, neither assertion is correct and as such, this basis for rejection is respectfully traversed.

Turning first to the description requirement, the Action notes that claims 1 and 11 recite a chimer having up to about 20 percent substituted amino acid residues in the HBc sequence, whereas claim 25 recites up to about 10 percent substitution. The Action calculates a molecule with about 30 substitutions at about 20 percent substitution. These numbers and an explanation are provided in the specification at pages 74 through the end of the section on page 76.

The Action alleges that there is a failure to provide necessary guidance that would lead to a substituted molecule. The Examiner's attention on the point to an alleged lack of guidance to the substitution issue is invited to end of the first full paragraph of page 74 that states:

> [g]uidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological activity or particle formation can be found using computer programs well known in the art, for example LASERGENE software (DNASTAR Inc., Madison, Wis.)

In addition, the last sentence of the last full paragraph of page 75 states:

> [s]ubstitutions, other than in the immunodominant loop of Domain II or at the termini, are preferably in the non-helical portions of the chimer molecule and are typically between residues 2 to about 15 and residues 24 to about 50 to help assure particle formation. See Koschel et al., (1999) *J. Virol.*, **73(3):**2153-2160.

That Koschel et al. article was noted in this Action.

The Zlotnick et al. paper noted at page 5 of the application and relied-on in the Action teaches that one can truncate the C-terminal thirty amino acid residues from HBc, change three internal cysteines into alanines, and still get particle formation.

It is yet further noted that a skilled worker would also look for guidance to Fig. 1 that contains six HBc sequences, of which four are from human viral strains. On examination of only the human viral sequences of that figure, one sees 17 positions of difference between the four viral sequences through residue 163. When the otherwise similar woodchuck and ground squirrel sequences are added, even more substitutions can be had.

In view of the above disclosures, it is submitted that the applicant was in possession of a very large number of the desired chimer molecules as of the filing date.

It is further submitted that when one looks at the Wands criteria he sees that there would be no undue experimentation here. Thus, the nature of the invention has to do with the most accurate replication system known to mankind, DNA technology for protein expression. The state of the art was

high, and the skill of those in this art was high. The above-noted art showed the great predictability of the out come of making changes to the sequences and certainly after the year 2000, workers knew well how to make and express proteins. The claim breadth is reasonable and guidance was provided. Working examples showing how to make and use the invention and various constructs were provided and the amount of experimentation needed should be small because people know now how to utilize this technology to achieve their ends.

The Action appears to put great reliance upon the disclosures of a paper by Rudinger, which was cited in the Action for the proposition that even one amino acid can make a major difference in the function of a molecule. However, it must be noted that that article was published in 1976. That date is years before the Cohen and Boyer patent on genetic engineering issued and more than a quarter century before this application was filed.

Workers of skill in this art have learned a great deal about proteins containing amino acid residue changes and their predictable expression since that time. For example, one need only look at the two citations on that topic noted above (LASERGENE and Koschel et al.). Still further on this point, the text has several additional citations concerning where and with what residues one can make substitutions such as the Pumpens and Borisova et al. *Intervirology* (1995) paper, those of Schödel and co-workers and those of Zlotnick et al. (1997). Thus, the present text and Fig. 1 of the application tell the skilled worker at the time of filing, whose ordinary skill of 2003-2004 would be more than that of a genius in 1976, where and with what residues one can make the substitutions.

Still further, the Rudinger paper deals with "peptide hormones". The peptide hormones discussed in Rudinger were nine or ten residues in length. Those peptides are short relative to the proteins considered here.

It is readily seen how a change of a single residue might have a drastic effect upon the efficacy of the molecule. One residue would be 10 percent or more of the molecule.

Here, the claimed molecules are much larger and a single residue is apt to have less of an effect. Indeed, more than 30 residues can be lopped from the C-terminus and the protein still self-assembles into particles. In addition, the Pumpens and Borisova et al. *Intervirology* (1995) article cited at pages 2, 6, 7, 50 and 77 of the specification and in the Action shows great numbers of inserts and deletions to the HBc sequence that can be made without ill effect. The Zheng et al., *J Biol Chem* **267**, 9422-9429 (1992) paper cited at least at page 132 of the present specification and noted in the Form PTO-892 states that that those authors mutated not only cysteine residues but also Leu^{60} to a Gly and Leu^{108} to Val and that those were "conservative changes which are expected to cause minimal change to the overall conformation of the mutant proteins" (at page 2423).

Still further, a hormone has an entirely different function from a molecule contemplated by the present invention. Hormones are sophisticated molecules that have matured over the millennia along with their receptors to carry out nature's chemistry of life. The present chimer molecules have a completely different blunt object-type effect on the body that typically only has to present an immunogen to immune cells,

which themselves are designed to take up foreign molecules. As such, a subtle change in sequence is of less impact here.

It is thus submitted that the Rudiger paper, being out of date and dealing with an entirely different type of subject matter, is in apt for this discussion, and reliance on its disclosures should be withdrawn, as should this basis for rejection.

D. Rejection Under 35 USC §102(b)

The pending claims were rejected as allegedly anticipated by the teachings of the paper by Zlotnick et al. (1997) (hereinafter Zlotnick). The Action has tried to characterize the Zlotnick disclosures in terms of the claims. However, the present amendments clearly distinguish the claimed subject matter from anything actually disclosed in Zlotnick. The differences between the presently claimed subject matter and that disclosed by Zlotnick are quite simple and will be discussed below.

Zlotnick made three pertinent HBc-like sequences and one hybrid. Those materials are shown schematically in Fig. 1a at the top of page 9557. From the top down, the first schematic construct shown is native HBc that was made by other than Zlotnick. The next construct made by Zlotnick, identified as Cp149, was C-terminally truncated to position 149 and contained the cysteines at their native positions of 48, 61 and 107. The second "new" Zlotnick-made construct is identified as Cp*149 that contains an alanine, "A", in place of each of the three above-noted cysteines, and was similarly C-terminally truncated. The third "new" Zlotnick-made construct was denominated Cp*150. That construct was similarly C-terminally truncated and had the

same three alanines replacing the three internal cysteines, as well as an added cysteine at C-terminal residue position 150. The last construct, the hybrid, included the protamine sequence from HBc position 150 through position 183 and is not germane to this discussion.

Thus, only construct Cp*150 contained a N- or C-terminal cysteine, but that structure had no added heterologous sequence added at the N-terminus, the C-terminus or in the immunogenic loop as is required by the present claims. Thus, none of the Zlotnick structures anticipates what is claimed here, and this rejection should be withdrawn.

The properties of that Zlotnick Cp*150 construct also provide no insight nor suggestion about another construct, such as that claimed herein that contains an added peptide-bonded epitope sequence. Indeed, the Schödel papers discussed in the paragraph bridging pages 6 and 7 of the specification note that instability is observed with C-terminally-truncated HBc proteins that contain insertions in their sequences as is claimed herein. Thus, the import of the heterologous residues whose presence is neither shown nor suggested by Zlotnick is that such residues are known in the art to cause instability. It is thus submitted that this rejection should be withdrawn.

E. Rejection Under 35 USC §102(a)

Claims 25, 27-28, 30, 32 and 43-46 were rejected as allegedly anticipated by the teachings of the paper by Jegerlehner et al. (2002) (hereinafter Jegerlehner). In view of the fact that Jegerlehner does not disclose a chimer contemplated by the claims, this rejection is respectfully traversed.

The relied-on disclosure teaches its constructs at page 3105. That disclosure teaches a HBc protein truncated to position 149 that further included cysteine mutations to serines at positions 48 and 107 and an added Gly-Gly-Lys-Gly-Gly sequence added between residues 72-88. That construct has no added cysteine residue at the N-terminus or C-terminus as is claimed. As such, this rejection should be withdrawn.

F. Rejections Under 35 USC §103(a)

1. First Rejection

Claims 2, 4-6, 16-22, 30-39 and 43-46 were rejected as allegedly obvious from the disclosures of Zlotnick (1997) above and Pumpens et al. (1995), hereinafter Pumpens. The Action discussed the Pumpens report of chimeras that contain a heterologous epitope discussed in Tables 1 and 3 of Pumpens. Unfortunately, Table 1 of the Pumpens paper relates to "full length" chimeras of HBc, not truncated chimeras as are claimed here. This is seen by the title of the Table that includes the words "full length". It is submitted that the stability behavior of truncated HBc molecules are so different from full length molecules that the latter are not predictive of the former. In addition, the Action provides no basis for making such a prediction.

The Action continued by reference to Pumpens at page 69, last paragraph, for a disclosure of "a heterologous linker residue for a conjugated epitope present in the HBC (sic) immunodominant loop." Unfortunately again, the "linker" discussed by Pumpens is the same type of "linker sequence" discussed in Borisova of Exhibit 4. That linker sequence is otherwise known as a polylinker, which is a nucleotide sequence

that contains one or more recognition sites for restriction endonucleases as are shown in Fig. 2 of the Borisova paper of enclosed Exhibit 5 in the regions coding for HBc positions 77-78 and after 144, respectively. It is respectively submitted that this rejection that is premised on two such mischaracterizations should be withdrawn without further discussion.

The Action continued with its discussion of the Pumpens disclosures to point out that Pumpens notes that "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." That statement was echoed by the later-published Borisova paper of Exhibit 5 that states near the top of the right-hand column of page 18 "HBcΔ (C-terminally-truncated HBc particles) were less stable than the corresponding full-length protein particles."

The Action also noted that Pumpens asserted that foreign insertions internal to the sequence "also exert an stabilizing effect on chimeric HBCΔ (sic) derivatives." The Action left out the basis for that statement, which was a parenthesized citation to unpublished results of Borisova, a co-author of the Pumpens paper. Interestingly, the Borisova paper of Exhibit 5 dealt with such internal insertions into HBc and reported no enhancement of stability. Thus, Borisova had an opportunity to report on the alleged enhanced stability and did not do so. To one skilled in the art, that fact from a published paper negates the comment from unpublished results.

On the other hand, the present inventors assert a lessening of stability with truncated HBc chimers that contain inserts that include the native cysteines at positions 48 and

107. This application has actual data in the examples that illustrate that instability, and further illustrate added stability for an otherwise identical chimer when those cysteines are absent. One skilled in the art would favor real data over a reference to unpublished results, particularly in view of the fact that the cited author of those unpublished results published on the underlying technology and made no mention of the alleged result.

The Action asserts that Zlotnick teaches that addition of a cysteine provided a stabilizing effect with two page citations. Thus, Zlotnick teaches in the Summary at page 9556 that addition of gold particles to an engineered mutant assembly domain provided a labeled protein unimpaired in its ability to form capsids. This construct was described in the text near the bottom of the right hand column of page 9556 just above "MATERIALS AND METHODS" was noted to have the three internal cysteines replaced by alanines and a new cysteine added at position 150. That construct was also referenced to Fig. 1a, as discussed previously.

The disclosure at page 9558 was somewhat more expansive, but still lacking as applied to the present claims. There, the same internal cysteine-lacking protein construct (Cp*150) with and with out gold was said to form capsids. The oxidized form of the cysteines was said to form oxidized disulfide-bonded dimers and the disulfides so formed stabilize the quaternary structure of the capsids. Of course, that comparison was made with the Cp*149 construct that had no cysteines at all. However, this disclosure says nothing about the effect of the absence of cysteines 48 and 107 on a truncated

HBc molecule that has its internal cysteines nor such a molecule that has an inserted sequence.

The Action concluded that a worker of ordinary skill would be motivated to combine the above teachings to arrive at the claimed subject matter. This conclusion also cannot be agreed with, even if the relied-on disclosures were as stated. Because the disclosures have been so incorrectly stated, the conclusion reached in the Action is still further from propriety. As was already noted, the sidebar assertion of Pumpens upon which so much weight is placed that sequence insertions cause HBc chimer particle stabilization is unsubstantiated by its ascribee, co-author Borisova, who had the opportunity and said nothing when he published thereafter on the same technology. Those assertions are further undermined by the sworn real data of the application that show a completely contrary result.

If one believed the unsubstantiated assertion of Pumpens, there would be no reason to add the C-terminal cysteines of Zlotnick by combining those teachings. Contrarily, the problem of instability would have been solved by inserting foreign sequences if Pumpens were correct. Of course, had the instability problem been solved as suggested by the Action, the problem alluded to in the application at page 9 and noted in Ulrich et al., *Adv. Virus Res.*, vol.50 (1998) Academic Press pages 141-182 (noted in the Form PTO-892), concerning "the requirement of reproducible preparation of intact chimer particles that can also withstand long-term storage" would have been met and Ulrich, writing three years after Pumpens, would have been mistaken.

Alternatively, if the skilled worker followed the good sense exhibited by workers of ordinary skill in science, and gave more credence to the later-published article of Ulrich over the earlier-published article of Pumpens that is cited in Ulrich, that worker would know that the problem of stability was not solved by inserting a heterologous sequence into the HBc sequence. Ulrich also cited the relied-on Zlotnick publication not having the present invention laid out before him did not suggest that stability could be achieved by combining those teachings. It is again submitted that this basis for rejection should be withdrawn.

Still further, and more to the point, the Action has misunderstood the invention. It has premised its arguments on the stabilizing effects of a C-terminal cysteine. Such a stabilizing residue can be and preferably is present. However, the added stability obtained in this invention is from the absence of the usually present cysteines at positions 48 and/or 107 when a C-terminal or N-terminal cysteine is also present. That point has not been addressed by the Action and is neither taught nor suggested by any of the art. This basis for rejection should therefore be withdrawn.

2. Second Rejection

Claims 7, 15 and 29 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995) in view of Zlotnick, (sic) et al. (1997) as applied previously and further in view of Nassal, M. et al. (1992). The rejection is traversed.

As was noted above, neither Pumpens nor Zlotnick teaches anything about added stability of a chimer when the

natural cysteines at positions 48 and 107 are removed and a stabilizing cysteine is present at either the N- or C-terminus. Nassal suggests that HBc chimers would be more stable with the cysteines at 48 and 107 present, and says nothing about adding back two cysteines at the recited positions 76 and 82, to say nothing of there being no disclosure concerning maintaining the cysteine deletions at 48 and 107 while adding cysteines at 76 and 82. As such, this rejection is also misdirected and should be withdrawn.

3. Third Rejection

Claims 2, 17, 30 and 31 were rejected as allegedly obvious from the combined disclosures of Zlotnick (above) in view of Nierynck et al., (1998) *Nature Medicine* **5(10):**1157-1163 (hereinafter Nierynck). The Nierynck paper teaches the use of the extracellular region of the M2 protein fused to the N-terminus of full length HBc. The region of the M2 protein utilized provided two cysteines near the N-terminus of the resulting chimer. Zlotnick is as described previously. The Action asserts that it would have been obvious to combine the two teachings "because Zlotnick teaches the production of more stable hepatitis B core particles via addition of C-terminal cysteine with concomitant removal of internal cysteine residues…" This basis for rejection cannot be agreed with and is respectfully traversed.

The Action has again misconstrued the Zlotnick teachings. It is submitted that the only comparison remotely related to the claimed stability that is taught by Zlotnick is that between the constructs referred to there as Cp*149 that was C-terminally truncated to position 149 and contained an alanine,

"A", in place of each of the cysteines at their native positions of 48, 61 and 107 and construct Cp*150 that was similarly C-terminally truncated and had the same three alanines replacing the three internal cysteines, as well as an added cysteine at C-terminal residue position 150. That comparison is shown in Fig. 2 and compares constructs that each lack cysteines at positions 48, 61 and 107, and one of which has a cysteine at the C-terminus. That is not the comparison recited in the claims that recite the presence or absence of cysteines at positions 48 and/or 107, and as such, this rejection should be withdrawn.

4. Fourth Rejection

Here, Claims 1-6, 8-14, 16-24, 26,31, and 33-42 were rejected over the disclosures of Jegerlehner as applied previously to claims 25, 27-28, 30, 32 and 43-46 in view of WO 01/9833 A2 to Page et al. (hereinafter Page). The Page teaching relates to a HBc chimer similar to that claimed here, but containing the cysteines at positions 48 and 107. The Jegerlehner teaching was discussed above and is basically a truncated and Cys^{48} and Cys^{107} mutated version of the HBc constructs discussed in US Patent No. 6,231,864 to one of the present inventors that is discussed at page 8 of the present specification.

The Action asserts that one would have been motivated to add the teachings of Page to those of Jegerlehner because Page "teaches that HBc core molecules as epitope carriers can be stabilized by the addition of C-terminal cysteines while also teaching the availability of numerous sites into which heterologous epitopes may be inserted." This conclusion cannot

be agreed with for several reasons and is respectfully traversed.

It is first noted that the Action misquoted Page by stating that Page teaches "[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a stable particle". The sentence actually was "[t]he removal of the arginine repeats reduces the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a disulfide bond which in the native structure is important for the formation of a stable particle".

The first error in the quote, changing "reduces" to "residues" was harmless because the sentence made no sense as written and one reading it would know that something was wrong. The second misquote was more pernicious because it could have made sense as written. That error was misleading and changed the intent of the disclosure. Thus, in the actual disclosure, the presence of the C-terminal cysteine is said to help stabilize the native molecule, whereas in the Action the cysteine was said to "allow for the formation of a stable particle". Those are two very different concepts in the context of this application because what may occur in the native molecule is not predictive and may or may not have an impact on a molecule having a different structure.

Additionally, the conclusion regarding motivation to combine the teachings was made based upon the misquoted phrase "because WO 01/98333 A2 teaches that HBc core (sic) molecules as epitope carriers may be made more stable by the addition of C-terminal cysteines..." It is submitted that there is no such

teaching, and because there is not, this improperly based rejection should be withdrawn.

Furthermore, it is submitted that there is no suggestion other than this application to combine the teachings of these two or any other disclosures. A key finding here is that changing two cysteines at positions 48 and 107 to other residues provides enhanced stability to a claimed chimer as compared to another chimer molecule having the same sequence but also having those two native cysteines.

A biochemist of ordinary skill would consider the presence of cysteine residues in a protein sequence to provide added stability to the protein's 3-dimensional or tertiary structure. Should the Examiner wish evidence that the cysteines in a protein contribute to tertiary structure and stability, counsel will be pleased to provide copies of texts that so state. Here, cysteines have been removed to provide enhanced stability. That is an unexpected and unpredicted result. This rejection should be withdrawn.

G. Provisional Double Patenting Rejection

All of the claims have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of five co-pending applications: (1) claims 1-78 of Serial No. 09/930,915; (2) claims 1-33 of Serial No.10/274,616; (3) claims 1-53 of Serial No. 10/787,734; (4) claims 98-109 of Serial No. 10/806,006 and claims 79-115 of Serial No. 10/806,006. The Action asserts that the claims are not patentably distinct from each other because claims 1-69 from an unnamed application are drawn to the same subject matter. Inasmuch as none of those applications is understood to be

allowed and which claims 1-69 are intended, it is believed premature to provide a terminal disclaimer for any or all of them at this time.

H. Summary

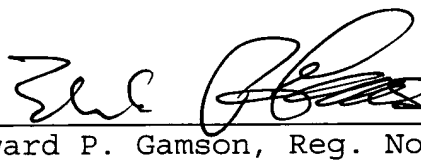
Claims 1, 11 and 25 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 

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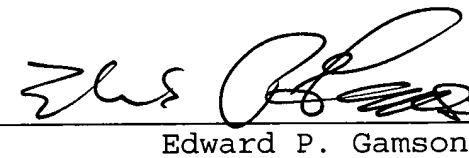
Exhibits 1-5

CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures, and a Petition for Extension of Time are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on May 16, 2005.

By 
Edward P. Gamson